



National FAQ on variations

9/12/2010



Important remark:

In case of questions about the Better Regulation on Variations, it is also advisable to have a look at the CMDh Q&A document and the list of published Article 5 Recommendations. You can find these documents at the following link: <http://www.hma.eu/96.html> and <http://www.hma.eu/293.html>.

The principles described herein also apply to the authorised medicines via the national procedure.

1. Glossary

- **MA:** marketing authorisation: all strengths and pharmaceutical forms of a particular product
- **SmPC:** summary of product characteristics
- **Labelling:** label and packaging (Word document)
- **MAD:** marketing authorisation document



2. Questions linked to the submission of variations

Question 2.1

On submission of a IA/IB variation affecting the SmPC, PIL and/or labelling, the adapted texts in Word version should be submitted in the national languages. What should happen in the situation where the registration procedure has not been dealt with yet at national level and consequently there are no texts available yet on which we can base ourselves?

Answer:

The last submitted version in the dossier that is not yet closed is used as a basis for the SmPC, PIL and labelling that need to be submitted when filing a type IA/IB.

This is only applicable for medicines authorised via MRP/DCP given that no variations can be submitted for medicines of which the NP has been approved but for which no MAD has been delivered yet.

Question 2.2

How should a grouping/worksharing be submitted?

Answer:

1 Grouping for 1 MA:

1 module 1 with among other things 1 cover letter + 1 common application form for the whole group (with clear enumeration of the individual variations in the group: number from the guideline + short description for each individual variation) + one module 2, 3, 4 or 5 (according to what applies) in which all requested modifications are included.

Different groupings for 1 MA:

For each grouping, a dossier complying with the above mentioned conditions needs to be submitted.

E.g.: for product A, one wants to submit a grouping composed of variations that have an impact on the active component as well as a grouping composed of variations that have an impact on the finished product: 2 separate dossiers for which, for each group, one module 1 and 3 must be submitted (and module 2 if applicable).

1 grouping for different MA: see our e-Submission Guideline, point 4 – Nice to Know, question 6. (http://www.fagg-afmps.be/en/human_use/medicines/Medicines/MA_procedures/esubmission/index.jsp)

Different groupings for different MA: For each grouping, a separate dossier, that complies with the description according to our e-Submission Guideline, point 4 – Nice to Know, question 6. ([http://www.fagg-](http://www.fagg-afmps.be/en/human_use/medicines/Medicines/MA_procedures/esubmission/index.jsp)



afmps.be/en/human_use/medicines/Medicines/MA_procedures/esubmission/index.jsp) needs to be submitted.

For annual reporting for different MA: one module 1 (and possibly module 2 or 3 if applicable) by MA.

For worksharing: see our e-Submission Guideline, point 4 – Nice to Know, question 6. (http://www.fagg-afmps.be/en/human_use/medicines/Medicines/MA_procedures/esubmission/index.jsp)

Question 2.3

Which numbering needs to be indicated in the application form for National groups of variations?

Answer:

For grouping, the company sets itself its n° when only one MA is concerned:
e.g.: NAT/H/254/IB/xxx/G

Where 254 is the Medicinal Product Number and xxx refers to the following n° in the list of the variations in the variation table. Given that for medicines authorised via NP, the serial number of the variation has often been just assigned on closing of the variation, the FAMHP asks to fill in xxx here.

In case of a grouping for different MA groups, the procedure number needs to be asked for to procedurenumber@fagg-afmps.be before submitting the dossier. Please indicate clearly in the e-mail which variations the grouping will consist of and which medicines will be included in the grouping.

The FAMHP will send you the requested procedure n° within a timeframe of 3 working days.

Question 2.4:

For which procedures does one must ask for a procedure n° and where can one do this?

Answer:

For the following procedures:

- NP: one IA or administrative variation for different MA and grouping of IA or administrative variations for different MA (e.g.: NAT/H/xxxx/IA/44/G)
- Worksharing with Belgium as reference authority (e.g.: BE/H/xxxx/WS/002)
- MRP BE=RMS: one IA-variation for different MA or grouping of IA for different MA. (e.g.: BE/H/xxxx/IA/12/G)



The procedure number can be asked for beforehand at the following e-mail address: procedurenumber@fagg-afmps.be. Please indicate clearly in the e-mail which variations the grouping will consist of and which medicines will be included in the grouping.

Question 2.5

When do the translations of the SmPC, PIL and labelling and packaging need to be submitted during a MRP and national procedure?

Answer:

	Type IA	Type IB	Type II
Submission of the translations	simultaneously with the submission of the dossier	simultaneously with the submission of the dossier	within 7 calendar days after the approval date

For Worksharing, the rule of the highest ranked type variation that is part of worksharing needs to be followed.

Question 2.6

How do little variations to the mock-up need to be submitted?

Answer

Type	Action towards FAMHP
Addition of a practical instruction symbol without other further modifications as regards content (e.g.: scissors + dotted line where to cut open the packaging)	<p><u>authorised via NP:</u> --> needs to be submitted as a notification (NP: art 34§4), adapted mock-up required, payment required</p> <p><u>Authorised via DCP/MRP:</u> --> if RMS requires notification: EU notification form (art 61.3) + adapted mock-up, payment required --> if RMS does not require notification: needs to be submitted as a notification at national level (NP: art 34§4), adapted mock-up required, payment required</p>
Addition of a logo or other non instruction oriented symbol	--> Submission of a EU/NP notification (art 61.3/art34§4) + adapted mock-up, payment required



<p>Modification as regards content (=modification to the content of the QRD template – labelling part)</p>	<p>Modification to the labelling is not linked to a modification to the SmPC: → Submission of a notification (unless variation n° C.1.1 or n° C.1.2 is applicable), adapted labelling texts in module 1.3.1 required, adapted mock-up required, payment required</p> <ul style="list-style-type: none"> - <u>authorised via NP: Art 34§4</u> - <u>Authorised via DCP/MRP: Art 61.3*</u> <p><i>* Excepting applications for derogations, specifically for Belgium. These ones must be asked for via a national Art 34§4 notification and should be included in the harmonized labelling afterwards.</i></p> <p>Modification to the labelling is linked to a modification to the SmPC: --> Submission of a variation, adapted labelling texts in module 1.3.1 required, payment required The modified mock-up is submitted with the variation or on closing of the variation</p>
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These notifications also need to be submitted to the Dispatching like for the other variations. Confirmation of receipt will be done via the automatic e-mails from MeseA.

The content of the dossier consists of a cover letter, application form (available on <http://www.hma.eu/101.html>), payment form, labelling (Word) as well as a mock-up proposal. Word documents need to be submitted out of the CTD structure in a separate folder.

Little modifications like colour change, lay-out change, rearrangement of the approved text or a combination of what precedes, must currently not be submitted to the Agency because of the workload. The readability of the packaging will be examined on following variation that has an impact on the label and packaging or at a five-year renewal.

The fee for this type of notification is set as follows:

- Modification only affecting the label and packaging: see section 4 National variation e) in the overview “ Registratie (en hernieuwing)”.
- Modification also affecting the PIL: see section 4 National variation d) second possibility in the overview “ Registratie (en hernieuwing)”.

You can find this overview on the Agency’s website on the following link:
<http://www.fagg-afmps.be/nl/home/items-home/bijdrage/index.jsp>.



3. Questions linked to the classification of the variations

Question 3.1:

How does a PIL-user testing need to be submitted?

Answer:

For NP and MRP: variation IB n° C.1.z

Question 3.2

How can SmPC, PIL and labelling be adapted to the QRD-template/SmPC-guideline?

Answer:

This adaptation can be done together with the submission of a type IB/II clinical variation with another subject.

However, when you only want to submit this adaptation – without submission of new data in support of the modifications - this can be done via NP and MRP with BE as RMS by means of a type IB by default n° C.1.z

Question 3.3

How should a division of common SmPC and labelling be submitted by dosage/pharmaceutical form?

Answer:

Via NP and MRP with BE as RMS: type IB by default n° C.1.z

Question 3.4

How should a variation for update of a complete module 3 be submitted?

Answer:

For national procedures, an update module 3 can be submitted as a type II (n° B.z). There is a specific fee for such a variation. The application form needs to clearly indicate that it concerns a complete update of module 3 and a clear overview of all changes included should be present.

This is not possible in MRP.



4. Questions linked to grouping and worksharing

Question 4.1

Is it according to the Belgian legislation possible to submit a grouping for products authorised via NP?

Answer:

yes

Question 4.2

is the FAMHP interested in groupings for products authorised via NP?

Answer:

yes

Question 4.3

Is it according to the Belgian legislation possible to apply worksharing for products authorised via NP?

Answer:

Yes, the Belgian legislation allows this. To allow products authorised via NP in a worksharing, the agreement of all concerned competent authorities is needed.

Question 4.4

Is Belgium interested by the application of worksharing for products authorised via the NP?

Answer:

Yes

Question 4.5

Is a grouping of variations also possible for different MA simultaneously?

Answer:

Only type IA variations can be grouped for different MA simultaneously. This group of type IA variations must then be the same for each MA and all MA should belong to the same MAH.

A grouping of variations, including one or several type IB/II variations for different MA simultaneously is only possible in Worksharing.



Question 4.6

What are the different grouping possibilities?

Answer:

For 1 MA:

→ grouping of different type IA variations (annual reporting)

→ grouping of a combination of IA/IB/II variations that is described in annex III of the Better Regulation or for which an agreement has been obtained from the competent authority.

For different MAs:

See question 4.5



5. Questions concerning the approval and implementation of the variations

Question 5.1:

When must and when can a variation be implemented?

Answer:

The variation can be implemented:

Type IA/administrative variations: do and tell: just before the submission for IA_{in} and national administrative variations and maximum 1 year before submission for the other IA. The implementation date must be indicated in the application form.

Type IB: date of submission + 44 days when no comments have been received from the FAMHP or date of submission of the answers + 30 days if no negative advice has been received.

Type II: 30 days after the approval of the procedure provided that the closing documents have been sent to the FAMHP. Exception: these variations that require an additional MAD.

Line extension: at the moment when the MAD is obtained.

Notification on the basis of art 34§4: 3 months after submission provided that no comments have been sent by the FAMHP or date of the approval by the FAMHP (via automatic round-up mail).

The variation must be implemented at the latest:

See art.35§4 of RD of 14.12.06.

Type IA/administrative variations: date of submission + 30 days + 6 months

Type IB: date of submission + 44 days + 6 months. Or if questions were raised: date of submission answer + 30 days + 6 months

Type II: approval date / date round-up mail + 6 months

Notification art 34§4: date of submission + 3 months + 6 months or date of approval (round-up mail) + 6 months

Question 5.2:

What is meant by “implementation date for IA variation”?

Answer:

See Q&A of the CMDh: question 5.2

Question 5.3:

When a company already implements a variation in the SmPC and PIL of the concerned product, what date of approval must then be indicated in the SmPC and PIL?

Answer:

The date of approval indicated in the SmPC and PIL is only entered by the FAMHP.



When the company wants to implement a variation, the date of approval should remain unchanged but the company should modify the date of last revision.

This date is determined as follows:

NP IA: date of implementation as indicated in the answer to question 5.2

NP IB: date of submission + 44 days when no comments have been received from the FAMHP or date of submission of the answers + 30 days

NP II: date of the round-up mail

MRP IA: date of implementation as indicated in the answer to question 5.2

MRP IB: approval date of the RMS

MRP II: approval date of the RMS

According to the QRD-template, the section “date of last revision” does not exist anymore. However this can be added to the PIL by the company when it implements a variation that hasn’t been administratively closed yet by the FAMHP.